GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION
SPONSORED PROJECT INITIATION

Date: 8/26/80

Project Title: Enhancing the Specificity of Synthetic Procedures

Project No: G-33-B08

Project Director: Dr. Herbert O. House

Sponsor: DHEW/PHS/NIH - National Institute of General Medical Sciences

Agreement Period: From 6/1/80 Until 5/31/81 (10 year)

Type Agreement: Grant No. 5-R01-GM20197-10

Amount: $141,206 PHS Funds (G-33-B08)
19,731 GIT Contribution (G-33-326)
$160,937 TOTAL

Reports Required: Annual Progress Reports with Continuation Applications;
Terminal Progress Report upon grant expiration

Sponsor Contact Person (s):

Technical Matters

Dr. A. E. Heming (Dr. Carl A. Kuether)
Associate Director for Program Activities
National Institute of General Medical Sciences
National Institutes of Health
Bethesda, MD 20014
*Phone: 301/496-7181

Contractual Matters
(thru OCA)

Evelyn W. Carlin (K. McKnight/M. J. C
Grants Management Officer
Office of Associate Director for
Program Activities
National Institute of General Medical
Sciences
National Institutes of Health
Bethesda, MD 20014
*Phone: 301/496-7166

NOTE: FOLLOW-ON PROJECT TO G-33-B07 (09 year)

Defense Priority Rating: None

Assigned to: Chemistry (School/~~Laboratory~~)

COPIES TO:

Project Director
Division Chief (EES)
School/Laboratory Director
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Project Code (GTRI)
Other

CA-3 (3/76)

GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

SPONSORED PROJECT TERMINATION

Date: August 20, 1981

Project Title: Enhancing the Specificity of Synthetic Procedures

Project No: G-33-B08

Project Director: Dr. Herbert House

Sponsor: DHEW/PHS/NIH - National Institute of General Medical Sciences

Effective Termination Date: 5/31/81

Clearance of Accounting Charges: -----

Grant/Contract Closeout Actions Remaining:

_ Final Invoice and Closing Documents
_ Final Fiscal Report
X Final Report of Inventions
_ Govt. Property Inventory & Related Certificate
_ Classified Material Certificate
X Other Annual Report of Expenditures due by 8/31/81

NOTE: Follow-on project (11 year) is G-33-B09

Assigned to: Chemistry (School/Laboratory)

COPIES TO:

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Other: _____

Georgia Institute of Technology
A UNIT OF THE UNIVERSITY SYSTEM OF GEORGIA
ATLANTA, GEORGIA 30332

CHEMISTRY

July 29, 1982

XC GIT
G33-B08
Terminal Report

Ms. Jane W. Julia
Office of Program Activities
National Institute of General
Medical Sciences
Bethesda, Maryland 20205

Re: Final Research Grant Report
NIGMS/OADPA
5R01-GM-20197

Dear Ms. Julia:

Enclosed please find a set of signed copies of the invention statement and a copy of the final progress report for the completed research grant referred above. Reprints of all publications except the last one (#46) have been mailed to your office previously. A copy of this final reprint will be sent to your office when it becomes available.

Sincerely yours,

Herbert O. House
Professor of Chemistry

Enclosures

HOH/lwn

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20205

July 19, 1982

Our reference: NIGMS/OADPA
5R01 GM20197-10

Dr. Herbert O. House
School of Chemistry
Georgia Institute of Technology
Atlanta, Georgia 30332

Dear Dr. House:

In the process of closing out the terminated grant referenced above, we note that the file does not contain a final progress report nor a final invention statement. Under Public Health Service policy we are unable to close out this account until these reports have been received.

We are enclosing the "guidelines" for the final progress report, which is to be a brief summary, and a set of final invention statement forms. Please note that the correct dates for the final invention statement are June 1, 1973, (the original effective date), and May 31, 1981, (the date of termination). After you have signed the final invention statement please forward to the appropriate institutional official for counter signature. When these reports are completed please mail them to me at the address given below.

Thank you for your assistance in the close out of this grant file. Should you have any questions please call me, (301) 496-7166.

Sincerely yours,

Jane W. Julia
Office of Program Activities
National Institute of General
Medical Sciences
Bethesda, Maryland 20205

enclosures

cc: Ms. Phyllis R. Oliver
JWJ/slh

OMB No. 0925-0159
Approved for use through 12/31/83

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FINAL INVENTION STATEMENT AND CERTIFICATION

(FOR GRANT OR AWARD)

DHHS GRANT OR AWARD NO.

5R01 GM20197-10

A. We hereby certify that, to the best of our knowledge and belief, all inventions are listed below which were conceived and/or first actually reduced to practice during the course of work under the above-referenced DHHS grant or award for the period

June 1, 1973 (original effective date) through May 31, 1981 (date of termination).

B. INVENTIONS (Note: If no inventions have been made under the grant or award, insert the word "NONE" under Title below.)

NAME OF INVENTOR	TITLE OF INVENTION	DATE REPORTED TO DHHS
	None	

Use continuation sheet if necessary)

C. FIRST SIGNATURE — The person responsible for the grant or award is required to sign (in ink). Sign in the block opposite the applicable type of grant or award.

TYPE OF GRANT OR AWARD	WHO MUST SIGN (title)	SIGNATURE
esearch Grant	Principal Investigator or Project Director	Herbert O. House
lealth Services Grant	Director	
esearch Career Program Award	Awardee	
ll other types *(specify)*	Responsible Official	

D. SECOND SIGNATURE — This block must be signed by an official authorized to sign on behalf of the institution.

TLE: Contracting Officer

PED NAME: Don D Hatley
or David R. Hendrix

GNATURE

DATE

NAME AND MAILING ADDRESS OF INSTITUTION

Georgia Institute of Technology
Atlanta, Georgia 30332

HS 568 (Rev. 12/81)

Final Progress Report for NIH Grant

Grant No.: NIGMS/OADPA 5R01-GM-20197

Principal Investigator: Herbert O. House

Institution: School of Chemistry, Georgia Institute of Technology

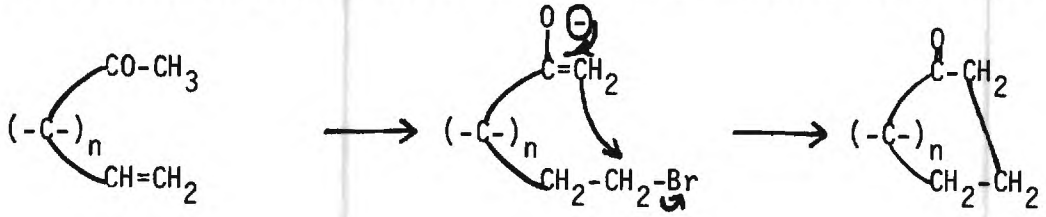
Grant Title: Enchancing the Specificity of Synthetic Procedures

Period Covered: June 1, 1973 to May 31, 1981

I. Summary of Research Progress (Superscripts refer to references listed in the following section.)

Our completed research in the area of metal enolate reactions includes (1) direct experimental evidence for the need to invoke a reactant-like transition state to explain the stereochemistry of alkylation reactions,[1] (2) the use of ^{13}C nmr and ^{1}H NMR measurement to predict and evaluate the reasons for reaction at O *vs* C in various solvents and with various cations,[19] (3) the use of metal chelates to control the structure and stereochemistry of aldols from regiospecifically generated enolates,[3,4,22] and (4) the finding that certain types of regiospecifically generated enolates can be used in Michael reactions under aprotic conditions.[22,25]

Our plan to prepare cyclic 6-membered or 7-membered ketones by the



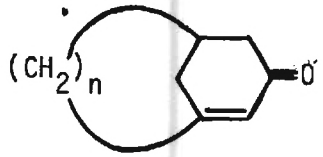
intramolecular alkylation scheme summarized in the accompanying equations has been developed[27,30,31,34] and is being used to prepare a series of perhydroazulene derivatives.[31,39] These perhydroazulenes are one group of a series of compounds being prepared[25,29,34,37,39] to explore the thesis that various remote groups can

influence (or control) the stereochemistry of various synthetic transformations by controlling the conformation of the substrate.

Continued study of organocuprate additions has revealed (1) a correlation between enone reduction potential and successful conjugate addition,[15] (2) at 25° the enone - cuprate product is a Li enolate not a Cu enolate,[24] (3) the need for careful temperature control with cuprates other than Me and Ph derivatives to avoid reduction and other side reactions,[5,11,15,27] and (4) the value of using $BrCu\text{-}SMe_2$ as a Cu(I) source for cuprate reagents.[15,27] Extensive study has been devoted to developing experimental tests that will distinguish whether various organometallic and carbanionic intermediates react by an ionic nucleophilic pathway or by pathway that involves an initial electron transfer step.[6,8,12-14,16,21-24]

We have completed our investigation of the effect of substituents and solvents on the conjugate addition of R_2CuLi reagents[32,36] and have demonstrated a clear-cut solvent effect that allows a chemist to suppress completely the normally rapid conjugate addition reaction with a polar aprotic solvent.[36] In this way the normally slow nucleophilic displacement reactions of R_2CuLi can be emphasized. Our further study of cuprates with conjugated cyclopropyl ketones[35] has demonstrated unambiguously that in this case opening of the cyclopropyl ring is nucleophilic displacement and does not involve rearrangement of a radical anion.

We have continued to make improvements in the methodology used to form hexahydrofluorene derivatives[28] and 1,8-diarylanthracene derivatives.[42] These improvements simplify further study of the chemistry of these systems. Our initial interest[26] in the rather special properties that might be found in enones with bridgehead double bonds has lead us to prepare a family of molecules[33,38,40,41,43,45,46] with the following structures:



(n = 3, 4, 5)

The more distorted members of this family have exhibited interesting behavior in cycloaddition reactions. We are continuing to study the molecular geometries and the unique chemistry of these molecules.

Finally in the area of perhydroindane derivatives we have (1) completed a total synthesis of recemic epiallogibberic acid,[3] (2) continued to explore and develop selective metallation reactions,[29] and (3) established that stereochemistry of alkylation of a dihydroaromatic anion can be directed by apropriate choice of the configuration of a nearby carboxylate group.[20]

II. Publication List

1. "The Chemistry of Carbanions. XXIV. Comparison of Stereochemistry in Alkylation and the Michael Reaction," Herbert O. House and Michael J. Umen, J. Org. Chem., 38, 1000 (1973).

2. "Derivatives of 1,8-Diphenylanthracene," Herbert O. House, Don Koepsell, and Wayne Jaeger, J. Org. Chem. 38, 1167 (1973).

3. "Perhydroindan Derivatives. XVI. The Synthesis of Racemic Epiallogibberic Acid," Herbert O. House and David G. Melillo, J. Org. Chem., 38, 1398 (1973)

4. "Chemistry of Carbanions. XXIII. Use of Metal Complexes to Control the Aldol Condensation," Herbert O. House, David S. Crumrine, Allan Y. Teranishi, and Hugh D. Olmstead, J. Amer. Chem. Soc., 95, 3310 (1973).

5. "The Chemistry of Carbanions. XXV. The Reaction of Various Organocopper Reagents with α, β-Unsaturated Carbonyl Compounds," Herbert O. House and Michael J. Umen, J. Org. Chem., 38, 3893 (1973).

6. "Reactions Involving Electron Transfer. V. Reduction of Nonconjugated Acetylenes," Herbert O. House and Edith Feng Kinloch, J. Org. Chem., 39, 747 (1974)

7. "Reactions Involving Electron Transfer. IV. Reduction of Enones with Chromium (II) Compounds, "Herbert O. House and Edith Feng Kinloch, J. Org. Chem., 39, 1173 (1974).

8. "Organocopper Reagents in Organic Synthesis," Herbert O. House, Proceedings of the Robert A. Welch Foundation Conferences on Chemical Research, November 5-7, 1973, Houston, Texas.

9. "The Chemistry of Carbanions. XXVI. The Synthesis of Certain γ-Alkenyl α, β-Unsaturated Ketones," Herbert O. House, Wei C. Liang, and Paul D. Weeks, J. Org. Chem., 40, 86 (1975).

10. "Some Stereochemical Aspects of the Claisen Rearrangement of Allyl Vinyl Ethers," Herbert O. House, Jacek Lubinkowski, and James J. Good, J. Org. Chem., 40, 86 (1975).

11. "Reduction as a Side Reaction Arising from the Thermal Decomposition of Lithium Organocuprates to Form Copper Hydride Derivatives," Herbert O. House and John C. DuBose, J. Org. Chem., 40, 788 (1975)

12. "Reactions Involving Electron Transfer. VI. A Stereochemical Test for Anion Radical Intermediates in Additions to Carbonyl Compounds," Herbert O. House and Paul D. Weeks, J. Amer. Chem. Soc., 97, 2770 (1975).

13. "Reactions Involving Electron Transfer. VII. Use of Intramolecular Reactions as a Test for Anion Radical Intermediates," Herbert O. House and Paul D. Weeks, J. Amer. Chem. Soc., 97, 2778 (1975).

14. "Reactions Involving Electron Transfer. VIII. The Reaction of Tritylllithium with Enones," Herbert O. House and Paul D. Weeks, J. Amer. Chem. Soc., 97, 2785 (1975).

15. "The Chemistry of Carbanions. XXVII. A Convenient Precursor for the Generation of Lithium Organocuprates," Herbert O. House, Chia-Yeh Chu, Joyce M. Wilkins, and Michael J. Umen, J. Org. Chem., 40, 1460 (1975).

16. "Use of Lithium Organocuprate Additions as Models for an Electron Transfer Process," Herbert O. House, Accts. Chem. Res., 9, 59 (1976).

17. "Cyclization of Unsaturated Hydroxylamine Derivatives," Herbert O. House, David T. Manning, David G. Melillo, Len F. Lee, O. R. Haynes, and Bruce E. Wilkes, J. Org. Chem., 41, 855 (1976).

18. "A New Synthesis of 2-Alkylpyrrolidines and 2-Alkylpiperidines," Herbert O. House and Len F. Lee, J. Org. Chem., 41, 863 (1976).

19. "The Chemistry of Carbanions. XXVIII. The Carbon-13 Nuclear Magnetic Resonance Spectra of Metal Enolates," Herbert O. House, Ananth V. Prabhu, and William V. Phillips, J. Org. Chem., 41, 1209 (1976).

20. "Perhydroindan Derivatives. XVII. Application of the Reduction-Methylation Sequence to 7-Methoxyhexahydrofluorene Derivatives," Herbert O. House, Roger C. Strickland, and Edward J. Zaiko, J. Org. Chem., 41, 2401 (1976).

21. "Reactions Involving Electron Transfer. 9. Reaction of Lithium Dimethylcuprate with Alkyl Aryl Ketones," Herbert O. House, Ananth V. Prabhu, Joyce M. Wilkins, and Len F. Lee, J. Org. Chem., 41, 3067 (1976).

22. "Reactions Involving Electron Transfer. 10. The Use of β-Cyclopropyl α, β-Unsaturated Ketones to Detect Anion Radical Intermediates," Herbert O. House and Karel A. J. Snoble, J. Org. Chem., 41, 3076 (1976)

23. "Reactions Involving Electron Transfer. 11. Reaction of Lithium Dimethylcuprate with Diaryl Ketones," Herbert O. House and Chia-Yeh Chu, J. Org. Chem., 41, 3083 (1976).

24. "The Chemistry of Carbanions. 29. The Nature of the Enolate Formed by Addition of Lithium Dimethylcuprate to Enones," Herbert O. House and Joyce M. Wilkins, J. Org. Chem., 41, 4031 (1976).

25. "The Chemistry of Carbanions. 30. Stereochemistry of the Metal-Ammonia Reduction of 7-tert.-Butyl-10-methyl-$\Delta^{1,9}$-octal-2-one," Herbert O. House and Michael J. Lusch, J. Org. Chem., 42, 183 (1977).

26. "Structure of the Substance $C_{27}H_{38}O$ Formed by the Base-Catalyzed Self-Condensation of Isophorone," J. Aaron Betrand, Duncan Cheung, Audrey D. Hammerich, Herbert O. House, Walter T. Reichle, Don VanDeveer, and Edward J. Zaiko, J. Org. Chem., 42, 1600 (1977).

27. "Synthesis of ω-Bromo Ketones," Herbert O. House, Chia-Yen Chu, William V. Phillips, Trevor S. B. Sayer, and Cheuk-Chung Yau, J. Org. Chem., 42, 1709 (1977).

28. "Perhydroindan Derivatives. 18. The Use of Indenone Ketals as Dienophiles," Herbert O. House and William C. McDaniel, J. Org. Chem., 42, 2155 (1977).

29. "An Efficient Synthetic Route to a Lactone Model for the Gibberellin a Ring," Herbert O. House and Edward J. Zaiko, J. Org. Chem., 42, 3780 (1977).

30. "Chemistry of Carbanions. 31. Cyclization of the Metal Enolates from ω-Bromo Ketones," Herbert O. House, William V. Phillips, Trevor S. B. Sayer, and Cheuk-Chung Yau, J. Org. Chem., 43, 700 (1978).

31. "Chemistry of Carbanions. 32. Formation of the Perhydroazulene System by Intramolecular Alkylation," Herbert O. House, Trevor S. B. Sayer, and Cheuk-Chung Yau, J. Org. Chem., 43, 2153 (1978).

32. "Reactions Involving Electron Transfer. 12. Effects of Solvent and Substituents upon the Ability of Lithium Diorganocuprates to Add to Enones," Herbert O. House and Joyce M. Wilkins, J. Org. Chem., 43, 2443 (1978).

33. "Enones with Strained Double Bonds: The Bicyclo [3.3.1] System," Herbert O. House, William A. Kleschick, and Edward J. Zaiko, J. Org. Chem., 43, 3653 (1978).

34. "Chemistry of Carbanions. 33. Use of Intramolecular Alkylation for the Stereospecific Formation of a cis-Decalone," Herbert O. House and William V. Phillips, J. Org. Chem., 43, 3851 (1978).

35. "Perhydroindan Derivatives. 19. Opening of a Cyclopropyl Ketone That Is Part of an Indanone System," Herbert O. House, William C. McDaniel, Ronald F. Sieloff, and Donald VanDerveer, J. Org. Chem., 43, 4316 (1978).

36. "Use of Dipolar Aprotic Solvents to Alter the Chemoselectivity of Lithium Dimethylcuprate," Herbert O. House and Thomas V. Lee, J. Org. Chem., 43, 4369 (1978).

37. "Chemistry of Carbanions. 34. Alkylation of a 1-Decalone Enolate with Abnormal Geometry," Herbert O. House, William V. Phillips, and Don VanDerveer, J. Org. Chem., 44, 2400 (1979).

38. "Enones with Strained Double Bonds. 2. The Bicyclo [4.3.1] decane System," Herbert O. House and Thomas V. Lee, J. Org. Chem., 44, 2819 (1979).

39. "Perhydroazulenes. 2. The 2-tert-Butylperhydroazulene-4-one System," Herbert O. House, Cheuk-Chung Yau, and Don VanDerveer, J. Org. Chem., 44, 3031 (1979).

40. "Enones with Strained Double Bonds. 3. Cycloadducts from Bicyclo-[3.3.1] non-1-en-3-one," Herbert O. House, Marvin B. DeTar and Don VanDerveer, J. Org. Chem., 44, 3793 (1979).

41. "Enones with Strained Double Bonds. 4. The Bicyclo [5.3.1] undecane System," Herbert O. House, Ronald F. Sieloff, Thomas V. Lee, Marvin B. DeTar and Don VanDeveer, J. Org. Chem., 45, 1800 (1980).

42. "Reactions of the 1,8-Diphenylanthracene System," Herbert O. House, Nabih I. Ghali, John L. Haack, and Don VanDerveer, J. Org. Chem., 45, 1807 (1980).

43. "Enones with Strained Double Bonds. 5. The 2-Methylbicyclo [3.3.1] non-1-en-one System," Herbert O. House, Marvin B. DeTar, Ronald F. Sieloff, and Don VanDerveer, J. Org. Chem., 45, 3545 (1980).

44. "Structure of a Byproduct Formed during Use of the Robinson Annulation Reaction with 6-Methoxy-1-methyl-2-tetralone," Ajoy K. Banerjee, Magaly S. Rizo, Miguel E. Alonso, Anibal Rojas, John L. Haack, Herbert O. House, and Don VanDerveer, J. Org. Chem., 46, 1755 (1981).

45. "Enones with Strained Double Bonds. 6. Cycloadditions with the Bicyclo [5.3.1] undecane and Bicyclo [4.3.1] decane Systems," Herbert O. House, Ronald F. Sieloff, and Don VanDerveer, J. Org. Chem., 46, 4639 (1981).

46. "Enones with Strained Double Bonds. 7. Precursors for Substituted Bicyclo [3.3.1] Nonane Systems, " Herbert O. House, Russell J. Outcalt, and Michael D. Cliffton, J. Org. Chem., 47, 2413 (1982).